B1 cont'd

outputting information about three-dimensional coordinates for each atom of the ligand in one or more stable docking structures including the most stable one relative to the biopolymer; as well as the stability of said docking structures, the binding modes and conformations of the ligand in said structures, wherein matching of distances among dummy atoms and those among heteroatoms of the ligand are tested, said dummy atoms being preset at the positions of the heteroatoms that can hydrogen-bond with hydrogen bonding groups in the biopolymer.

7. A method which comprises:

inputting three-dimensional coordinates for each atom of a biopolymer as well as atomic element, bond-type of covalent bonds and three-dimensional coordinates for each atom of a ligand;

selecting possible docking structures between said biopolymer and said ligand while changing the conformation of said ligand; and

outputting information about three-dimensional coordinates for each atom of the ligand in one or more stable docking structures including the most stable one relative to the biopolymer, as well as the stability of said docking structures, the binding modes and conformations of the ligand in said structures, wherein matching of distances among dummy atoms and those among heteroatoms of the ligand are tested, said dummy atoms being preset at the positions of heteroatoms that can hydrogen-bond with hydrogen-bonding groups in the biopolymer.

8. A method which comprises:

inputting three-dimensional coordinates for each atom of a biopolymer as well as atomic element, bond-type of covalent bonds and three-dimensional coordinates for each atom of a ligand;

covering possible docking structures between said biopolymer and said ligand while changing the conformation of said ligand; and

outputting information about three-dimensional coordinates for each atom of the ligand in one or more stable docking structures including the most stable one relative to the biopolymer, as well as the stability of said docking strutures, the binding modes and conformations of the ligand in said structures, wherein matching of distances among dummy atoms and those among atomes of the ligand are tested, said dummy atoms being preset at the positions of atoms that can specifically interact with functional groups in the biopolymer.

9. A method which comprises:

inputting three-dimensional coordinates for each atom of a biopolymer as well as atomic element, bond-type of covalent bonds and three-dimensional coordinates for each atom of a ligand;

selecting possible docking structures between said biopolymer and said ligand while changing the conformation of said ligand; and

outputting information about three-dimensional coordinates for each atom of the ligand in one or more stable docking structures including the most stable one relative to the biopolymer, as well as the stability of said docking structures, the binding modes and conformations of the ligand in said structures, wherein matching of distances among dummy atoms and those among atoms of the ligand are tested, said dummy atoms being preset at the positions of atoms that can specifically interact with functional groups in the biopolymer.

10. A method for estimating stable docking structures between a biopolymer and a ligand, wherein possible docking structures are selected by matching of distances among dummy atoms and those among heteroatoms of the ligand, said dummy atoms being preset at the positions of heteroatoms of the ligand that can be hydrogen-bonded with hydrogen

bonding groups in the biopolymer.

11. A method for estimating stable docking structures between a biopolymer and a ligand, wherein possible docking structures are selected by matching of distances among dummy atoms and those among atoms of the ligand, said dummy atoms being preset at the positions of atoms of the ligand that can specifically interact with functional groups in the biopolymer, while changing the conformation of the ligand.--

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IN THE ABSTRACT

Please replace the Abstract with the new Abstract of the Disclosure provided on the attached page.

SUPPORT FOR AMENDMENTS

Claims 6-11 are now active in this application. These claims are supported by the specification and claims as originally filed. The new Abstract provided is likewise supported by the original application as filed and obviates the Examiner's objection to the Abstract. No new matter has been added by these amendments.

REQUEST FOR RECONSIDERATION

The present invention provides methods for the determination of the most energetically favorable docking structures between a biopolymer (such as a protein) and a ligand having one or more atoms that can interact with functional groups in the biopolymer, or one or more hydrogen bonding heteroatoms. An important factor in each claim is that these atoms or heteroatoms in the ligand that either interact with functional groups in the biopolymer or provide hydrogen bonding sites are each designated to correspond to a dummy

atom. Hence the dummy atoms used in the present method correspond in space to the atom or heteroatom itself. Also, there can be multiple dummy atoms in the present method, since the ligand can have multiple atoms that interact with biopolymer functional groups or multiple hydrogen bonding heteroatoms present (see figures).

The claims stand rejected under 35 U.S.C. 101. Applicants respectfully traverse this rejection on the grounds that the Examiner clearly has misapplied the statute. The Examiner states that the claims are drawn to a series of steps to search for a stable docking molecule, which uses mathematical steps and can therefore be accomplished merely by mental steps. However, the Examiner belies this position by then using in prior art rejections the U.S. patent 4,855,931 to Saunders. This patent, although completely different in the particular steps performed in the method, also describes a method for determining a likely structure of a molecule, the steps of which also involve so-called "mathematical" steps that could ostensibly be performed mentally. By making this rejection, the Examiner has essentially questioned the validity of the Saunders patent, as well as a large number of other patents based upon calculation containing steps.

What the Examiner appears not to realize is that the present method provides a "useful, tangible" result, namely a determination of the most stable docking structure of a ligand with a biopolymer. Such a result is useful in further design of drugs that interact with the same active site of the biopolymer by knowing the spatial geometry of the locus, or by design of a biopolymer having an active locus that will interact with the same ligand. Accordingly, the Examiner's rejection is improper and should be withdrawn.

The claims further stand rejected under 35 U.S.C. 102 over Pattou et al, or under 35 U.S.C. 103 over Saunders in view of Tong. None of the references cited by the Examiner teach or suggest a key feature of the present claims as now amended, namely the reference

never designates actual atoms in the ligand as the dummy atoms, nor the designation of multiple atoms in the ligand as dummy atoms. In fact, the references disclose methods that do not use a "dummy atom" approach at all. Pattou disclose molecular modeling programs that go through various torsion angles, bending parameters, and stretching parameters in order to find the lowest energy conformations of a molecule or combination of molecules (docking program). While the ultimate outcome of the Pattou method could be the same as that of the present invention, the steps used to get there are not. In the present method, the dummy atoms correspond to the actual locations of heteroatoms in the ligand that undergo hydrogen bonding with the biopolymer, or the dummy atoms correspond to actual locations of atoms in the ligand that interact with a functional group on the biopolymer. Pattou, on the other hand, makes no use or discussion of designating "dummy atoms" within any molecule, and certainly does not do this in the docking calculations. Accordingly, Pattou cannot anticipate the present invention.

Saunders describes a stochastic approach to conformational analysis in which the X, Y and Z coordinates of the atoms in a particular molecule are varied by combining them with random numbers to create a new random coordinate position for each atom. This is not, however, the same as designating the actual atoms of the molecule as dummy atoms as required in the present invention. In fact, the method described in Saunders does not make use of the dummy atom approach at all. Tong et al do not overcome the deficiencies of Saunders, since Tong also does not use a dummy atom approach, as required by the present claims. Tong describes a method for determining structural effects of binding of amine drugs with the diphenylmethyl functionality of a cyclodextrin. Again, while the ultimate outcome of the method of Tong might coincide with the outcome of the present method, namely the determination of a most stable docking structure, the method used is not the same, nor even

suggestive of the present invention. Tong makes no disclosure or teaching regarding the designation of certain atoms as dummy atoms in the amine ligand. Rather the approach used by Tong is merely an iterative approach calculating various energies of conformations, without the use of a dummy atom approach. Since this use of dummy atoms is a requirement of the present invention as now claimed, neither Saunders nor Tong, either alone or in combination, can render the present invention obvious, since neither of these references suggests the designation of certain atoms in the ligand as dummy atoms in the calculations. Accordingly, the rejections should be withdrawn.

The claims also stand rejected under 35 U.S.C. 112, first paragraph. This rejection is respectfully traversed on the grounds that the specification clearly enables one of ordinary skill in the art to practice the invention without undue experimentation. In particular, the specification teaches the person of ordinary skill how to proceed with designation of dummy atoms and how to vary the torsion angles, bond angles, etc. in order to determine stability of various docking structures. While Applicants disclose AMBER as a program that can perform these calculations, it is not the only one that can be used, and was merely presented as an example. As an indication that other programs that can perform the same type calculations are well known in the art, one needs turn no further than the references cited by the Examiner, which disclose various molecular modeling programs such as AMBER, BIOGROMOS, MOL3D and SYBYL. While it is true that each of these programs differs from the others in some way, those of skill in the art know the benefits and abilities of the programs available. All that is needed is to pick the program that one wants to use and which has the ability to calculate the parameters desired. This is clearly within the level of ordinary skill and requires no undue experimentation. Applicants have enabled the method as claimed, since it is only necessary to determine which atoms to designate as dummy atoms,

then using the desired calculation program, determine the energies of various docking structures to find the most stable. Accordingly, the rejection should be withdrawn.

The claims further stand rejected under 35 U.S.C. 112, second paragraph. This rejection is likewise traversed on the grounds that the claims as stated are clear and definite. Certain of the claims recite a step of "covering" the docking structures. These claims require that the program look at all or nearly all permutations of docking structures between the ligand and biopolymer, given the specified dummy atoms and their general areas of interaction. Alternatively, other claims require the selection of "stable docking structures" followed by varying certain parameters, to determine an ultimate most stable structure. The Examiner has queried why one would "destabilize" a selected "stable docking structure". In the area of molecular modeling, it is common practice to have multiple structures that are stable in themselves, with only one of these being the most stable. By varying the parameters of these stable docking structures, it is possible to determine when the structure is merely in an intermediate energy well, and when the structure is in the lowermost energy well (i.e. the most stable structure). If a structure is stable, but not the most stable, by varying the parameters, it is possible to have the structure remove itself from the local minimum energy well and travel along the energy path to the most stable structure. If calculations were carried out on all such stable structures (which is not required by the claims, but is illustrative of the point), and allowed to proceed to minimization of each structure, it is possible to have each structure ultimately end up at the same "most stable docking structure". Accordingly, altering parameters of a stable docking structure in order to determine which stable structure is the most stable is well understood in the molecular modeling art. Accordingly, these rejections should be withdrawn.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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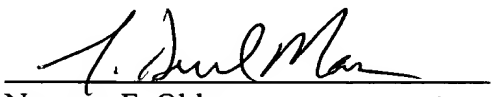

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